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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,851	MASHKO ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/09/02; 05/03/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms, which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: page 3, line 13 ("has been appeared earlier"), line 27 ("more complicate situation could be occurred..."); p. 5, l. 10 ("The later leads...), l. 17 ("providing increase of the controlled gene expression"); p. 6, ll. 1, 11 ("provides not decrease, but increase..."); p. 17, l. 14 ("base paring"); p. 46, l. 1 ("The each strain..."), l. 9 ("suspension as the sample...").

In the Brief Explanation of the Drawings beginning on page 11, the descriptions for the various drawings must correspond in detail to the figure parts or subparts. For example, Fig. 3 has parts (a) – (c), but the description only refers to the general scheme depicted in Fig. 3a.

Figures 5-8 disclose sequences that are not properly identified with sequence identifiers (i.e. "SEQ ID NO:"). Sequence Listing, See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02. If said sequences were originally submitted in both electronic and paper format, then applicant is only required to make proper amendment to the Brief Description of the Drawings (i.e. with proper sequence identifiers). However, if applicant has not previously submitted said sequences, then a new submission is also required (i.e. CD-ROM/CD-R, Written Format, Attorney Declaration). Appropriate correction of the foregoing is required.

Claim Objections

Claims 2 and 3 are objected to because of the following informalities: The claim appears to contain a typographical error (i.e. "paring", claim 2, line 21; claim 3, lines 2, 7, 12, 14, 16). It would be very much appreciated if applicant would review the claims to correct any additional typographical errors. Appropriate correction is required.

Claim 9 contains "an1", "an2", "an3", "an4" and "an5". When using acronyms, the corresponding definition for the term should be properly introduced.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The claims are generally narrative and indefinite, failing to conform to current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors. The following are illustrative and not comprehensive examples:

For example, claim 1 recites, "bacterium which harbors a DNA construct comprising ...frequency of termination in the expression control sequence, of transcription starting from the promoter". As written the claim is vague and indefinite, because it is unclear how a DNA construct can comprise a "frequency of termination". The claim appears to be a composition of

various sentence fragments that in total confer ambiguity and impreciseness, in regard to the claim's metes and bounds.

Claim 2 recites, "[DNA construct comprises]...leader peptide comprising said amino acid ... wherein when translation of the leader peptide stops at codon of said amino acid in the course of the translation in case of starvation of said amino acid, a base paring [sic] structure forms in the [ECS transcript], whereby the frequency of termination in the expression control sequence, of the transcription increases". Claim 2 is simply incomprehensible as written.

Claim 3 recites, "not less than 3, of segments... ". This claim is difficult to interpret and understand. Another illustrative example is claim 4, which recites, "wherein the first segment overlaps with codon of the amino acid... ". The claim is vague and indefinite because it is unclear which segment is the "first segment".

In sum, the claims seem to be a composition of sentence fragments put together in a disjointed fashion, leading to difficulty in delineating the claims' metes and bounds. The claims should be reviewed and revised to comply with 35 U.S.C. 112, second paragraph (i.e. using proper grammar and idiom).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in**

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to products and processes incorporating hairpin-dependent or rho-independent structures in regulating target gene expression, as correlated to an intracellular amino acid concentration. Base claim 1 is drawn to a genus of "expression control sequences" (ECS) which control expression of linked target genes based on intracellular concentration of any amino acid. Claims (9-10) that further particularize the ECS structure are drawn to genera of either tryptophan- or histidine-derived sequences. Therefore the claims are drawn to genera of any ECS as well as any ECS "derived" from tryptophan or histidine operons. In addition the ECS can be responsive to any amino acid in any bacterial species. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification provides a specific embodiment, as depicted in figures 2A, which constitute a single species. In addition, a single species of bacterium (*E. coli*) is used to perform protein expression assays (e.g. Example 2, pp. 44-46). The art teaches that different bacteria even within a genus of bacteria may have different amino acid requirements. It logically follows, that different bacteria would have operons or biosynthetic mechanisms that have disparate responses to concentrations of different amino acids. (e.g. Chopin, A. FEMS

Microbiology Reviews, 1993; 12: 21-38; at page 22: noting several species of *Lactococcus* with different amino acid requirements; at page 27: noting transcription terminators of rho-independent nature). Therefore, particular regulatory ECS would not necessarily be interchangeable from one bacterial species to the next. In addition, engineered amino acid-attenuation/anti-termination operons, even within the same species, may or may not effect amino acid-induced expression of downstream target genes. For example, sequence specificity in the stem loop structure of RNA hairpins can influence transcription termination. (e.g. Jeng et al. Can. J. Microbiol. 1997; 43:1147-1156, at page 1152). Furthermore, there may be promoter-specificity with respect to particular regulatory sequences (i.e. ECS). (Id. at p. 1153, Table 2). Therefore, there would unpredictability with regard to both the different species of ECS, as well as within different species of bacteria. In other words, all ECS species could not operate in the prescribed manner in all bacteria.

The disclosure, in light of what is known in the art, is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all ECSs based on the teachings in the specification. For example, the sequences characterized as ECS can number in the thousands, with even single base changes conferring functional alterations. Furthermore, a sequence characterized as "derived from" a particular operon does little to apprise the ordinary skilled artisan of the actual structure correlating with the prescribed function. The disclosure merely defines "derived from" as being a sequence that is similar to the native sequence. As the invention shows with regard to the specific species disclosed (Fig. 2A, No. 3: "Artificial TrpHis anti-attenuator), a construct having similar sequences to the native operons, alters the regulatory function diametrically from one of a

default antitermination amino acid-induced attenuation to one of default attenuation amino acid-induced antitermination. Moreover, there may be interplay between the particular bacterium and the particular species of ECS disclosed, where for example an ECS that is functional in one bacterium is not necessarily functional in another bacterium.

Given the enormous breadth of the ECS encompassed by the rejected claims, and given the limited description from the instant specification of such ECS, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus of ECS. An applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 1 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Gish and Yanofsky (J. Bacteriol. 1995; 177(24:7245-54; see whole document; hereinafter Gish).

The claims are drawn to a product and process comprising a promoter, a control expression sequence and a target sequence, where an increase in expression correlates to increasing intracellular amino acid concentrations.

Gish teaches an expression control sequence (tryptophanase operon (*tna*)) in *E. coli* where elevated levels of an amino acid (tryptophan) induces transcription of a target gene (tryptophanase). More particularly, Gish teaches a vector construct that contains a *tet* promoter or *tna* promoter upstream of an ECS (*tnaC* operon) and a target gene (tryptophanase or *lacZ*). (e.g. p. 7248, col. 1). As a result of tryptophan addition to culture media, target gene expression was increased significantly. (e.g. p. 7248, Table 3).

4. Claims 1-3, 5-6 and 11-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Lu et al. (J. Bacteriol. Jan. 2001; 183(2):490-99; see whole document).

The claims are drawn to an Expression Control Sequence (ECS) comprising a promoter and target gene, where target gene expression is regulated by an intracellular amino acid concentration. The ECS has at least 3 segments wherein adjacent segments can form base pairing structures, where in one of the at least 3 segments overlaps with an amino acid codon, where at least part of each segment (sequence) constitutes an inverted repeat. With respect to claims drawn to particular "segments" (claims 3-6), the claims are interpreted as broadly as reasonable in light of the vague and indefinite claim language. Therefore, a segment is interpreted to mean at least the number of nucleotides capable of forming a base pair structure in a construct comprising an ECS. Furthermore, the ECS can comprise any sequence that qualifies as a "leader peptide" of any length; any part within such a sequence can have an inverted repeat sequence, as claim 6 recites "part thereof" in this context.

Lu et al. teach a construct comprising a promoter linked upstream of an expression control sequence (gdhB operon) linked to a downstream target gene (*gdhB*). (e.g. p. 492, Fig.

2(a)). In addition, the gdhB regulatory region comprises a rho-independent terminator. (Id.). The construct was used to transform bacteria, wherein subsequent increasing concentrations of an amino acid (arginine) resulted in increased target gene production (28-fold increased NAD-GDH activity). (e.g. p. 492, col. 2, ¶ 1; p. 495, Fig. 5(a)). The regulatory operon taught comprises at least 3 segments capable of forming base pair structures (e.g. p. 492, Fig. 2(b)). The sequence taught contains an inverted repeat sequences (Id. "GTTG", in sequence line "70"). Lu et al. anticipate the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER